or, in the case of injectables, with each dose administered to the patient. This section does not preclude the manufacturer or labeler from distributing additional patient labeling pieces to the dispensor.

(3) Patient package inserts for estrogens dispensed in acute-care hospitals or long-term care facilities will be considered to have been provided in accordance with this section if provided to the patient before administration of the first estrogen and every 30 days thereafter, as long as the therapy continues.

(c) *Patient package insert contents.* A patient package insert for an estrogen drug product is required to contain the following information:

(1) The name of the drug.

(2) The name and place of business of the manufacturer, packer, or distributor.

(3) A statement regarding the benefits and proper uses of estrogens.

(4) The contraindications to use, i.e., when estrogens should not be used.

(5) A description of the most serious risks associated with the use of estrogens.

(6) A brief summary of other side effects of estrogens.

(7) Instructions on how a patient may reduce the risks of estrogen use.

(8) The date, identified as such, of the most recent revision of the patient package insert.

(d) *Guidance language.* The Food and Drug Administration issues informal labeling guidance texts under § 10.90(b)(9) of this chapter to provide assistance in meeting the requirements of paragraph (c) of this section. Requests for a copy of the guidance text should be directed to the Center for Drug Evaluation and Research, Division of Metabolism and Endocrine Drug Products (HFD–510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

(e) *Exemptions.* This section does not apply to estrogen-progestogen oral contraceptives. Labeling requirements for these products are set forth in § 310.501.

(f) *Requirement to supplement approved application.* Holders of approved applications for estrogen drug products that are subject to the requirements of this section must submit supplements under § 314.70(c) of this chapter to provide for the labeling required by paragraph (a) of this section. Such labeling may be put into use without advance approval by the Food and Drug Administration.

[55 FR 18723, May 4, 1990]

§ 310.516 Progestational drug products; labeling directed to the patient.

(a) The Commissioner of Food and Drugs concludes that the safe and effective use of any progestational drug product requires that patients be informed that there is an increased risk of birth defects in children whose mothers have taken this drug during the first 4 months of pregnancy. Accordingly, except as provided by paragraph (d) of this section, any progestational drug product that is the subject of a new drug application approved either before or after October 9, 1962 and all identical, related, or similar drug products as defined in § 310.6, whether or not the subject of an approved new drug application, shall be dispensed to patients with labeling in lay language containing such a warning. The patient labeling shall be provided as a separate printed leaflet independent of any additional materials.

(b) The patient labeling shall specifically include the following:

(1) Name of the drug.

(2) Name and place of business of the manufacturer, packer, or distributor.

(3) A warning that there is an increased risk of birth defects in children whose mothers take this drug during the first 4 months of pregnancy.

(4) A brief discussion of the nature of the risks of birth defects resulting from the use of these drugs during the first 4 months of pregnancy.

(5) A brief statement that these drugs are no longer considered safe as a test for pregnancy.

(6) A statement that the patient should inform her physician as soon as possible if she discovers that she was pregnant when she took the drug.

(c) The patient labeling shall be printed in accordance with the following specifications:

(1) The minimum letter size shall be one-sixteenth of an inch in height.

(2) Letter heights pertain to the lower-case letter ''o'' or its equivalent that shall meet the minumim height standard.

(3) Type used shall conform to the minimum letter height. The body copy shall contain 1-point leading, noncondensed type, and shall not contain any light-face type or small capital letters.

(d) This section does not apply to a progestogen-containing product intended for contraception, which shall be labeled according to the requirements of § 310.501.

(e)(1) Patient labeling for each progestational drug product shall be provided in or with each package intended to be dispensed to the patient. Patient labeling for drug products dispensed in acute-care hospitals or long-term care facilities will be considered to have been provided in accordance with this section if provided to the patient before first administration of the drug and every 30 days thereafter, as long as the therapy continues.

(2) In the case of progestational drug products in bulk packages intended for multiple dispensing, a sufficient number of patient-labeling pieces shall be included in or shall accompany each bulk package to assure that one can be included with each package dispensed to every patient. Each bulk package shall be labeled with instructions to the dispenser to include one patient-labeling piece with each package dispensed to the patient. This section does not preclude the manufacturer or labeler from distributing additional patient-labeling pieces to the dispenser.

(3) In the case of progestational drug products for injection, each package shall include a sufficient number of patient-labeling pieces for the volume of the vial, and instructions to the practitioner administering the drug to give one patient-labeling piece to each premenopausal woman, except those in whom childbearing is impossible, receiving the drug.

(4) This section does not apply to oral dosage forms labeled solely for the treatment of advanced cancer.

(5) Any progestational drug product, except as noted in paragraphs (d) and (e)(4) of this section, that is not labeled as required by this section and is either introduced or delivered for introduction into interstate commerce, or held for sale after shipment in interstate commerce, is misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act. However, a progestational drug product in the possession of a wholesaler or retailer before December 12, 1978, is not misbranded if adequate numbers of copies of the patient labeling are furnished to the wholesaler or retailer to permit any retail purchaser after that date to obtain such labeling with the product. The requirement that any progestational drug product be dispensed with patient labeling, as applied to physicians who dispense or administer the drug, will not be effective for supplies in their possession on the effective date, but will apply only to supplies received thereafter.

(f) The Food and Drug Administration has available guideline patient labeling for progestational drug products that includes information responsive to all items specified in paragraph (b) of this section. This labeling was published in a separate notice appearing in the FEDERAL REGISTER of January 12, 1989. Any person may rely on this labeling as complying with paragraph (b) of this section.

(g) Holders of approved new drug applications for progestational drug products that are subject to the requirements of this section shall submit supplements under § 314.70(c) of this chapter to provide for the labeling required by paragraph (a) of this section.

[43 FR 47181, Oct. 13, 1978, as amended at 46 FR 53657, Oct. 30, 1981; 54 FR 1163, Jan. 12, 1989]

§ 310.517 Labeling for oral hypoglycemic drugs of the sulfonylurea class.

(a) The University Group Diabetes Program clinical trial has reported an association between the administration of tolbutamide and increased cardiovascular mortality. The Food and Drug Administration has concluded that this reported association provides adequate basis for a warning in the labeling. In view of the similarities in chemical structure and mode of action, the Food and Drug Administration also believes it is prudent from a safety standpoint to consider that the possible increased risk of cardiovascular mortality from